

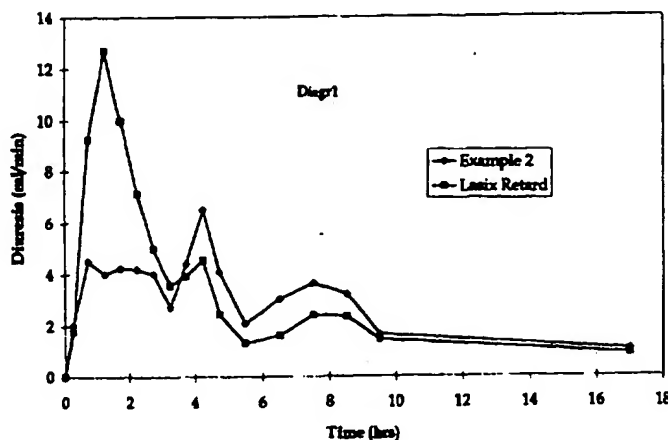


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(54) Title: PHARMACEUTICAL CONTROLLED RELEASE BEADS COMPRISING FUROSEMIDE AND A FORMULATION CONTAINING SAID CONTROLLED RELEASE BEADS

Mean diuresis vs midpoint of each time interval (n=12)



(57) Abstract

The present invention relates to controlled release beads comprising a core of an insoluble or soluble inert material provided with a layer of furosemide dispersed in a hydrophilic polymer and a specific outer membrane for controlled release of the furosemide whereby the membrane comprises 1) a film former selected from ethyl cellulose and copolymerisates of acrylic and methacrylic acid esters and 2) at least one hydrophilic polymer selected from polyvinylpyrrolidone, hydroxypropyl cellulose and polyalkylene glycols; in that the amount of the outer membrane is between 35 and 65 % (w/w) based on the dry layered core; and in that the release profile of furosemide is not more than 30 % after 60 minutes, not more than 44 % after 120 minutes and more than 80 % after 360 minutes. The present invention also refers to a process for the preparation of said controlled release beads, a pharmaceutical formulation comprising said beads and the use of said beads for treatment of cardiovascular diseases such as hypertension, congestive heart failure and oedema.

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PHARMACEUTICAL CONTROLLED RELEASE BEADS COMPRISING FUROSEMIDE AND A FORMULATION CONTAINING SAID CONTROLLED RELEASE BEADS

Field of the invention

The present invention relates to pharmaceutical controlled release beads comprising furosemide and a formulation containing said controlled release beads suitable for the treatment of cardiovascular diseases such as light to medium severe hypertension, congestive heart failure and oedema. The formulation has favourable release characteristics compared to conventional dosage forms, thereby providing an attractive dosage form without inconvenient side effects, for long term treatment of hypertension with furosemide.

Background of the invention

Medical treatment of certain physiological conditions e.g. hypertension, often requires a continuing medication for a long period of time, and the patient is thereby often submitted to a life long treatment, which requires a simple and convenient dosage regimen with respect to ease of use and acceptable levels of side effects.

Hypertension is frequently treated by the administration of diuretics, e.g. furosemide.

Furosemide is a loop diuretic which is preferably used in the long term treatment of cardiac oedema, or oedema of light to medium severe degree. However, furosemide is also used for the treatment of a light to medium severe hypertonia, particularly when there is diminished kidney function, or diabetes. Furosemide is also used in case of congestive heart failure.

Furosemide is an acid with a pKa-value of 3.9, and furosemide is normally characterised (USP XXIII) as being practically insoluble in water, soluble in acetone and in alkaline water solutions, which means that furosemide exhibits a pH dependent solubility.

Administration of furosemide orally, in a conventional dosage form, results in an immediate and substantial diuretic effect within the first hours after administration. The use of

furosemide for the treatment of hypertension thereby adds specific demands on the furosemide formulation, with respect to the rapid onset of diuresis produced by the substance per se. In order to reduce the rapid onset of diuresis produced by furosemide the controlled release formulation has to be formulated giving a reduced initial diuresis while, at the same time maintaining the effect on hypertension. This means, that the release profile of furosemide obtained from the controlled release dosage form has to be balanced between the disadvantages with the immediate increase in diuresis after an oral administration, and the advantages of the reduction in human blood pressure induced by furosemide.

It is therefore highly desirable to have a controlled release furosemide formulation, intended for treatment of hypertension, with an even diuresis profile and a low total diuresis. It is therefore an object of the present invention to provide a controlled release formulation comprising furosemide, suitable for the treatment of hypertension, avoiding the high initial diuresis peaks usually experienced with dosage forms of furosemide on the market.

15

The intention of controlled release formulations is to provide an extended duration of the pharmacological response after administration of the dosage form, than is ordinarily experienced after the administration of an immediate release dosage form. The purpose of these formulations is to provide a constant concentration of the active substance in body fluids for a certain time period. However, the demand on controlled release dosage forms is immense, the maximal therapeutically effect is to be reached using a minimum amount of active substance to reduce the frequency of and the degree of side effects, as well as inter- and intra individual effect variations.

Controlled release beads are preferably based on the use of polymeric membranes by which the release of the active substance is modified and controlled. Generally a polymeric membrane consists of a film former and additives such as hydrophilic polymers, plasticizers and pigments, and release of the active substance occurs according to various release profiles, e.g. pH dependent, pH independent, with or without lag time.

One important type of controlled release polymeric membranes are membranes giving a pH independent release of active substance in the range of pH 1-8. Within this pH range the film former has substantially no solubility and the release of the active substance occurs as a consequence of diffusion through the polymeric membrane. The release rate is thereby
5 primarily governed by the solubility and partition of the active substance into the polymeric membrane, the thickness of the polymeric membrane and the porosity of the polymeric membrane.

The invention provides a solution to the above mentioned problem in that it relates to a
10 controlled release formulation comprising controlled release beads containing furosemide, giving a significant reduction in blood pressure while the diuresis produced by the formulation is minimised, and resembles the natural diuresis profile experienced in patients. The invention thus provides a possibility to balance the desired pharmacological response, i.e. the depression of human blood pressure produced by furosemide, with the negative
15 undesired side effects such as a rapid onset of diuresis.

Prior art

US patent 4,324,779 describes a method for treating hypertonia with a preparation of furosemide having a slightly retarded release. The furosemide-containing pellets which are
20 filled into hard gelatine capsules, essentially consist of a core of furosemide having thereover a sustained release coating which starts to dissolve in a weakly acid medium.

US patent 4,888,179 describes a multiple-unit dose composition comprising furosemide which is characterised by specified release rate in pH 1.5, 5.5 and 7.5. The composition
25 consists of spherical granules coated with an inner layer consisting of ethyl cellulose and hydroxypropylmethyl cellulose and an outer layer consisting of hydroxypropyl methyl cellulose phthalate.

US patent 4,983,401 describes a sustained-release preparation utilizing a pH controlled
30 diffusion membrane composed of a pH sensitive film-forming polymer. The film forming

polymer is hydrophobic at pH range as found in the stomach and hydrophilic at pH range as found in the intestines.

PCT/FI92/00242 describes a long-acting pharmaceutical composition comprising a core
5 containing the active ingredient in rapid release form and a coating containing the active ingredient in slow release form.

EP 475 536 describes a technique of coating cores with a spraying powder containing an active drug and low substituted hydroxypropyl cellulose. The granules obtained exhibit
10 increased granule strength and improved disintegration properties.

US patent 4,713,248 describes a controlled release multiple unit formulation containing an active substance coated with a water based film comprising a homogeneous combination of water-dispersible film forming agent and a polymeric substance which impart
15 compressibility to the coating.

US patent 4,938,968 describes a controlled release formulation containing pellets of indometacin of only one type. The pellets relates indometacin in both immediate and sustained release form.

20

Outline of the invention

We have now surprisingly found that the problems mentioned above, i.e. an uneven diuresis profile including a significant initial increase in diuresis after administration of furosemide, is solved by the new pharmaceutical controlled release beads according to the present
25 invention by using the minimum amount of furosemide needed for maximal therapeutical effect, thereby maintaining the diuresis on a level which resembles the common diuresis cycle in patients. Said controlled release beads comprise a core of an insoluble or soluble inert material provided with a layer of furosemide dispersed in a hydrophilic polymer and coated with an outer membrane comprising a film former selected from ethyl cellulose and
30 copolymerisates of acrylic and methacrylic acid esters and at least one hydrophilic polymer selected from polyvinylpyrrolidone, hydroxypropyl cellulose and polyalkylene glycols,

whereby the amount of the outer membrane is between 35 and 65% (w/w) based on the dry layered core and the release profile of furosemide is not more than 30 % after 60 minutes, not more than 44 % after 120 minutes and more than 80 % after 360 minutes.

5 As already mentioned above the film former is selected from ethyl cellulose and copolymerisates of acrylic and methacrylic acid esters (e.g. Eudragit® RL, Eudragit® RS). In the case of using different qualities of acrylic resins as the film former the permeability of the polymeric membrane is imparted by choosing different qualities of the acrylic resins, such as Eudragit® RL, Eudragit® RS in varying portions or a combination of the acrylic
10 resins. Organic solutions or water-based dispersions of the film former, as will be appreciated by a person skilled in the art, could be used for obtaining the membrane. Preferred film former is ethyl cellulose.

The hydrophilic polymer which is incorporated into the polymeric membrane, to adjust the
15 permeability of the polymeric membrane, is selected from polyvinylpyrrolidone, polyalkylene glycols and hydroxypropyl cellulose of which hydroxypropyl cellulose is the most preferred one. The preferred polyalkylene glycol is polyethylene glycol.

The amount of hydrophilic polymer in the outer membrane is between 20 and 50 % (w/w).
20 A preferred amount of hydrophilic polymer in the outer membrane is between 30 and 45% (w/w), a more preferred amount of hydrophilic polymer in the outer membrane is between 35 and 45% (w/w). The most preferred amount of hydrophilic polymer in the outer membrane is between 32 and 39% (w/w), specially between 35 and 39% (w/w).

25 A preferred amount of the hydrophilic polymer in the outer membrane is 35-45% (w/w) and is most preferred 35-39 % (w/w) if the hydrophilic polymer is hydroxypropyl cellulose, 25-35 % (w/w) if the hydrophilic polymer is a combination of hydroxypropyl cellulose and polyvinylpyrrolidone and 35-45 % (w/w) if the hydrophilic polymer is polyethylene glycol.

The combination of the film former ethyl cellulose and the hydrophilic polymer hydroxypropyl cellulose as the outer membrane is found to be favourable for obtaining a favourable release profile of furosemide from the controlled release beads.

- 5 It has been found that coating of dry furosemide layered cores with 35-65 % (w/w) polymeric (outer) membrane is needed in order to enable a favourable release profile and thereby a favourable diuresis profile and also to enable compression of the beads in a tablet formulation, also including pharmaceutically acceptable excipients, or filling hard gelatine capsules. Preferably is the amount 45-55 % (w/w) used for obtaining a favourable release
10 profile of furosemide from the controlled release beads.

The hydrophilic polymer in which furosemide is dispersed is conventional, such as polyvinylpyrrolidone, polyalkylene glycol, gelatine, polyvinyl alcohol, starch and derivatives thereof and cellulose derivatives.

15

The insoluble or soluble inert material of which the cores are made is also conventional and may be sugar spheres or sand particles (silicone dioxide). By inert material means a non-pharmacologically active material. The particle size of the cores is preferably about 0.1-0.3 mm.

20

Preferred controlled release beads comprise a sand core provided with a layer of furosemide dispersed in polyvinylpyrrolidone and coated with an outer membrane comprising 55-65% (w/w) ethylcellulose and 35-45% (w/w) hydroxypropyl cellulose.

- 25 Another preferred type of controlled release beads is beads comprising a sand core provided with a layer of furosemide dispersed in polyvinylpyrrolidone and coated with an outer membrane comprising 55-65% (w/w) ethylcellulose and 35-45% (w/w) polyethylene glycol.

- Still another preferred type of controlled release beads is beads comprising a sand core
30 provided with a layer of furosemide dispersed in polyvinylpyrrolidone and coated with an

outer membrane comprising 65-75% (w/w) ethylcellulose and 25-35% (w/w) of a combination of polyvinylpyrrolidone and hydroxypropyl cellulose.

Due to the limited solubility of furosemide at gastro-intestinal pH 1-8, the release profile
5 obtained by using a controlled release polymeric membrane consisting solely of a film
former is totally inadequate in obtaining a clinical significant result. However, it has been
found that by incorporating a hydrophilic polymer within the film former higher permeability
is imparted to the polymeric membrane. Thus, the release profile of furosemide from the
controlled release formulation can be monitored, controlled and adjusted to give the
10 pharmacologically desired result in patients. This means that the release profile of
furosemide from the controlled release beads according to the invention is primarily
governed by the choice of and the proportion of the hydrophilic polymer within the film
former and the total amount of film former and hydrophilic polymer applied onto the
furosemide layered cores.

15 The invention also provides a novel, controlled release formulation comprising furosemide,
having clinical and pharmaceutical advantages, thereby providing a pharmaceutical
formulation for treatment of cardiovascular diseases, such as light to medium severe
hypertension, congestive heart failure and oedema, with limited undesired side effects, such
20 as rapid onset of diuresis. The controlled release furosemide formulation comprises beads
according to the invention described above optionally together with pharmaceutically
acceptable excipients. The formulation is in the form of tablets or capsules. The
pharmaceutical characteristics allow the controlled release beads to be transformed into
controlled release tablets, maintaining the release profile of furosemide after compression of
25 the controlled release beads, and hence no altering of the bioavailability and clinical effect
occurs. Thus, the formulation according to the invention in the form of tablets or capsules
has the same release profile as the beads according to the invention.

The pharmaceutical formulation provided by the invention is characterised by the specific
30 composition of the controlled release membrane, the total amount of the controlled release

membrane constituents applied onto the furosemide layered core, the release profile of furosemide from the controlled release beads and by the diuresis profile thereby obtained.

The invention described above produces a controlled release rate of furosemide
5 characterised by the specified USP XXIII paddle method for in vitro release of an active substance. The characterisation is carried out at a pH of 6.8 and a stirring speed of 100 rpm. The release of furosemide from the beads and from the formulation comprising said beads thereby provided by the invention is not more than 30 %, preferably about 3-30%, after 60 minutes, not more than 44%, preferably about 10-44%, after 120 minutes and more than
10 80 % after 360 minutes.

One specific aim of the invention is to provide a formulation which gives an even diuresis profile and a low total diuresis, compared to commercially available furosemide formulations. The diuresis profile after administration of a single dose comprising 60 mg
15 furosemide of the invention in a clinical survey, is characterised by a low and extended diuresis with no substantial fluctuations in the diuresis. Comparing the diuresis profiles produced by the invention with data of the diuresis profiles obtained by available relevant formulations comprising furosemide support these findings.

20 Pharmaceutical formulations

The formulation above comprising controlled release beads with a release controlling membrane may be prepared by conventional methods such as fluidized beds with top-spray or Wurster techniques or powder layering techniques, or any technique well known to one skilled in the art. The insoluble or soluble inert core particles, such as sand particles, are
25 provided with a layer of a dispersion comprising furosemide and a hydrophilic polymer applying a conventional fluid bed top-spray technique. The so formed furosemide layered cores are subsequently coated with the polymeric membrane, comprising a film former and a hydrophilic polymer applying a conventional fluid bed Wurster technique.

Plasticizers may be added to the polymeric membrane in order to improve the technical
30 properties of the membrane or modify the release characteristics. Examples of plasticizers that may be used are citrate esters, acetylated monoglycerides, and glycerinetriacetate or

any other conventional plasticiser usable for film preparation as will be clear to anyone skilled in the art.

When the controlled release beads are compressed into tablets they are blended with
5 pharmaceutically acceptable excipients to obtain favourable filling, binding, lubrication and
disintegration properties. Examples of excipients are microcrystalline cellulose, lactose,
spray dried lactose, dicalcium phosphate, pregelatinized starch, starches and derivatives
thereof such as sodium starch glycolate and maltodextrine, sorbitol, maltitol, cellulose and
derivatives thereof, polyethylene glycol, polyvinyl pyrrolidone, compressible sugar, stearic
10 acid, magnesiumstearate, sodium stearyl fumarate, talc, colloidal silicone dioxide or any
other conventional excipient usable for tablet preparation as will be clear to anyone skilled
in the art.

The excipients comprised in the tablet, together with the controlled release beads, may be
15 used as direct compression excipients or they may be granulated into granules with
favourable compression and flow characteristics. Disintegrants may or may not be added.
Lubricants will normally be added. The amount of excipients, eventually granulated into
granules, may be in the range from 25 to 75 % (w/w) of the total tablet weight. To obtain
even more favourable compression characteristics the proportion of excipients should be
20 between 40 and 75 % (w/w) of the total tablet weight.

The amount of furosemide in the pharmaceutical formulation according to the invention is in
the range 10 -100 mg, preferably in the range 30 - 70 mg, more preferably in the range
40 -60. the most preferred formulations have an amount of furosemide of 60 mg or 30 mg.

25

The following examples will describe, but not limit, the invention.

Examples

30

Layered cores:

Silicone dioxide (0.1-0.3 mm)

800 g

Water, purified	1500 g
Furosemide (90%<10µm)	800 g
Polyvinyl pyrrolidone, K-30	400 g

- 5 In a fluidized bed granulator furosemide dispersed in a solution of polyvinyl pyrrolidone (K-30) in water was sprayed onto sand (silicone dioxide).

Coating solutions:

Example 1

10	Ethyl cellulose	260 g
	Hydroxypropyl cellulose	140 g
	Ethanol	3500 g

Example 2

15	Ethyl cellulose	258 g
	Hydroxypropyl cellulose	142 g
	Ethanol	3500 g

Example 3

20	Ethyl cellulose	256 g
	Hydroxypropyl cellulose	144 g
	Ethanol	3500 g

Example 4

25	Ethyl cellulose	252 g
	Hydroxypropyl cellulose	148 g
	Ethanol	3500 g

Example 5

30	Ethyl cellulose	248 g
	Hydroxypropyl cellulose	152 g

Ethanol	3500 g
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Example 6

Ethyl cellulose	240 g
5 Polyethylene glycol	160 g
Ethanol	3500 g

Example 7

Ethyl cellulose	280 g
10 Hydroxypropyl cellulose	60 g
Polyvinylpyrrolidone	60 g
Ethanol	3500 g

800 g of the dry layered cores formed, as described above, were coated with ethyl cellulose
15 and hydroxypropyl cellulose, by spraying a solution of the mentioned substances in ethanol.

Composition for one tablet containing 60 mg furosemide

Coated beads (Ex. 1-7)	225.0 mg
20 Microcrystalline cellulose (Avicel® PH 200)	337.5 mg
Sodium starch glycolate	22.5 mg
Magnesium stearate	0.06 mg

Controlled release beads described in Example 1-7 were mixed with microcrystalline
25 cellulose, and further mixed with sodium starch glycolate. Magnesium stearate was
admixed, and the mixtures were compressed into tablets in a single punch tablet press at a
compression force of 10 kN (\pm 1 kN) at a compression speed of not more than 70 tablets
per minutes. Flat faced punches with a diameter of 11 mm were used.

The tablets disintegrated within 30 seconds in 1000 ml purified water at 37°C liberating the
30 controlled release beads.

The in vitro release, in accordance with USP XXIII Paddle method, 1000 ml buffer solution with pH 6.8, of the tablets compressed at 10 kN, containing 60 mg furosemide, is shown in Table 1.

5 **Table 1**

Percent released furosemide from the controlled release tablets, in accordance with USP XIII paddle method, at pH 6.8 (n=3)

10	Examples	<u>Percent released furosemide after</u>					
		30	60	120	180	240	360
		(min)					
	1	5	10	26	46	70	86
15	2	5	10	30	56	81	100
	3	4	10	33	62	86	100
	4	5	14	44	76	92	
	5	3	11	44	80	98	
	6	12	23	42	59	74	92
20	7	6	12	28	48	69	96

Conclusion

25

The invention described herein provides a reproducible and controllable rate of release of the active ingredient, furosemide, by applying a specified amount of the specified controlled release membrane comprising a film former and a hydrophilic polymer. The invention described herein has favourable characteristics for the treatment of hypertension in that it gives a total diuresis after oral administration resembling the normal diuresis level experienced by patients, thereby rendering the controlled release formulation comprising furosemide suitable for the long term treatment of hypertension.

30

The diuresis profiles shown in Figure 1, are taken from a controlled clinical trial on 12 healthy human subjects comparing the formulation according to the invention and a reference furosemide retarded release product existing on the Swedish market, namely Lasix[®] Retard[®] depot capsules which according to SWEDIS contain furosemide, sucrose, stearic acid, ethanol, ethyl acetate, Shellac, polyvidonum, aluminium hydroxide gel and starch maize. It is clearly shown that the formulation according to the invention has significant and favourable characteristics with respect to the diuresis. The diuresis resembles the normal diuresis experienced by a patient, i.e. the diuresis profile, as a result of the invention, provides an even diuresis profile over a certain time period and the clinically undesirably high initial diuresis peak has been deleted by the present invention, thereby rendering the controlled release dosage form substantial advantages for long term treatment with furosemide for conditions such as hypertension.

CLAIMS

1. Controlled release beads comprising a core of an insoluble or soluble inert material provided with a layer of furosemide dispersed in a hydrophilic polymer and coated with an
5 outer membrane **characterised** in that said outer membrane comprises
 - 1) a film former selected from ethyl cellulose and copolymerisates of acrylic and methacrylic acid esters and
 - 2) at least one hydrophilic polymer selected from polyvinylpyrrolidone, hydroxypropyl cellulose and polyalkylene glycols;
- 10 in that the amount of the outer membrane is between 35 and 65% (w/w) based on the dry layered core; and in that the release profile of furosemide is not more than 30 % after 60 minutes, not more than 44 % after 120 minutes and more than 80 % after 360 minutes.
2. Controlled release beads according to claim 1 **characterised** in that said film
15 former is ethyl cellulose.
3. Controlled release beads according to any one of claims 1-2 **characterised** in that the hydrophilic polymer of the membrane is hydroxypropyl cellulose.
- 20 4. Controlled release beads according to any one of claims 1-3 **characterised** in that the hydrophilic polymer of the membrane is polyethylene glycol.
5. Controlled release beads according to any one of claims 1-4 **characterised** in that the hydrophilic polymer of the membrane is a combination of hydroxypropyl cellulose
25 and polyvinylpyrrolidone.
6. Controlled release beads according to any one of claims 1-5 **characterised** in that the amount of the hydrophilic polymer in the outer membrane is between 20 and 50 % (w/w).

7. Controlled release beads according to any one of claims 1-6 **characterised** in that the amount of the hydrophilic polymer in the outer membrane is between 30 and 45 % (w/w).
- 5 8. Controlled release beads according to any one of claims 1-7 **characterised** in that the amount of the hydrophilic polymer in the outer membrane is between 35 and 45 % (w/w).
9. Controlled release beads according to any one of claims 1-7 **characterised** in
10 that the amount of the hydrophilic polymer in the outer membrane is between 32 and 39 % (w/w).
10. Controlled release beads according to any one of claims 1-9 **characterised** in that the amount of the hydrophilic polymer in the outer membrane is between 35 and 39 %
15 (w/w).
11. Controlled release beads according to any one of claim 1-6 **characterised** in that the amount of the hydrophilic polymer in the outer membrane is 35-39 % (w/w) if the hydrophilic polymer is hydroxypropyl cellulose, 25-35 % (w/w) if the hydrophilic polymer is
20 a combination of hydroxypropyl cellulose and polyvinylpyrrolidone and 35-45 % (w/w) if the hydrophilic polymer is polyethylene glycol.
12. Controlled release beads according to any one of claims 1-11 **characterised** in that the core is made of sand (silicone dioxide).
- 25 13. Controlled release beads according to any one of claims 1-12 comprising a sand core provided with a layer of furosemide dispersed in polyvinylpyrrolidone and coated with an outer membrane comprising 55-65% (w/w) ethylcellulose and 35-45% (w/w) hydroxypropyl cellulose.

14. Controlled release beads according to any one of claims 1-12 comprising a sand core provided with a layer of furosemide dispersed in polyvinylpyrrolidone and coated with an outer membrane comprising 55-65% (w/w) ethylcellulose and 35-45% (w/w) polyethylene glycol.

5

15. Controlled release beads according to any one of claims 1-12 comprising a sand core provided with a layer of furosemide dispersed in polyvinylpyrrolidone and coated with an outer membrane comprising 65-75% (w/w) ethylcellulose and 25-35% (w/w) of a combination of polyvinylpyrrolidone and hydroxypropyl cellulose.

10

16. A process for the preparation of controlled release beads according to any one of claims 1-15 characterised in that furosemide dispersed in a solution of a hydrophilic polymer, sprayed onto the insoluble or soluble inert cores giving a layer of furosemide and thereafter the outer membrane is sprayed onto the furosemide layer.

15

17. A pharmaceutical formulation comprising controlled release beads according to any one of claims 1-15, optionally together with pharmaceutically acceptable excipients.

20

18. A pharmaceutical formulation according to claim 17, wherein the amount of furosemide is in the range 10 - 100 mg.

19. A pharmaceutical formulation according to claim 18, wherein the amount of furosemide is in the range 30 - 70 mg.

25

20. A pharmaceutical formulation according to claim 19, wherein the amount of furosemide is in the range 40 - 60 mg.

21. A pharmaceutical formulation according to claim 20, wherein the amount of furosemide is 60 mg.

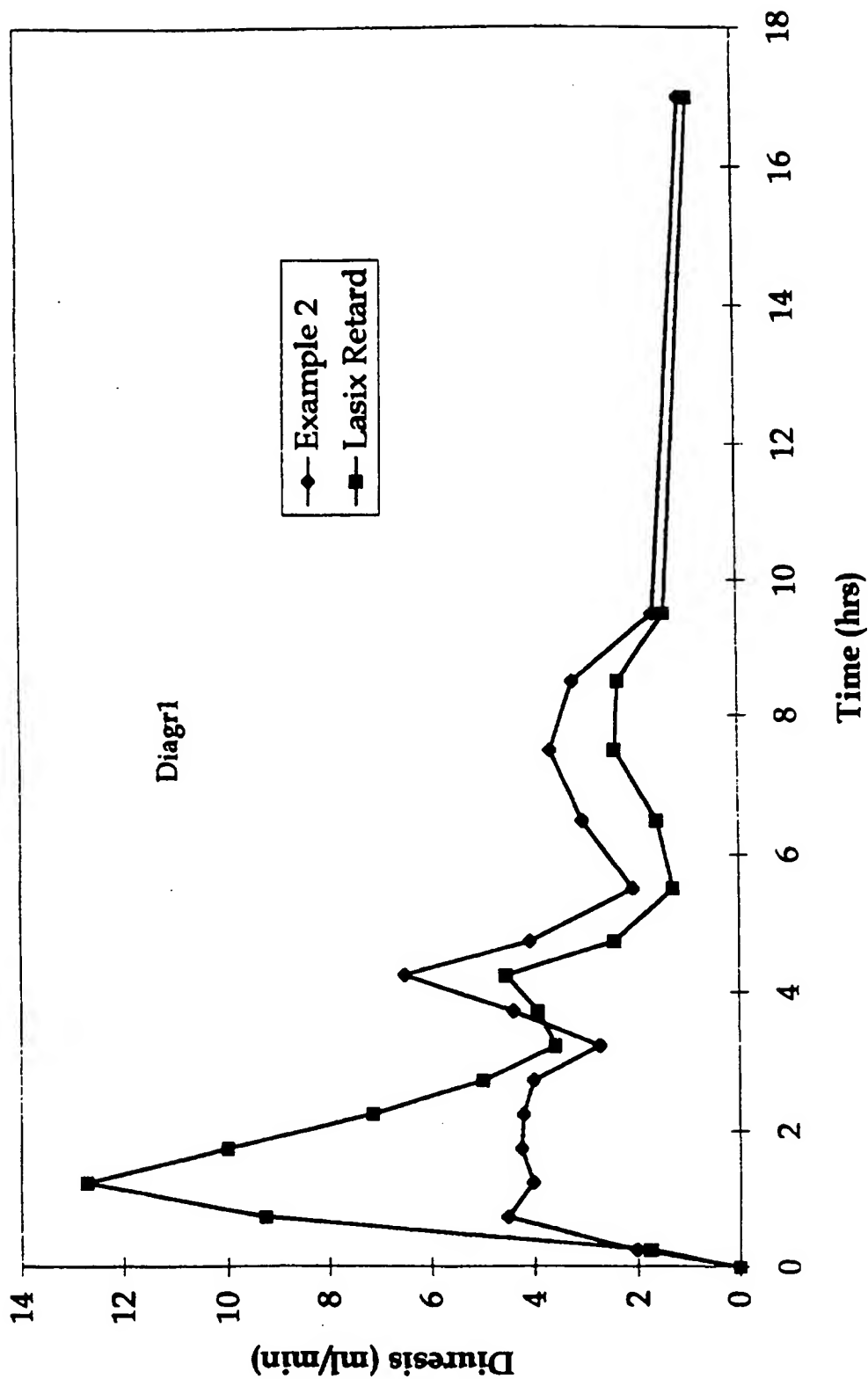
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22. A pharmaceutical formulation according to claim 21, wherein the amount of furosemide is 30 mg.
23. A pharmaceutical formulation according to any one of claims 17-22 in the form of
5 tablets.
24. A pharmaceutical formulation according to any one of claims 17-22 in the form of capsules.
- 10 25. A process for the manufacture of a pharmaceutical formulation according to any one of claims 17-23, wherein the beads are compressed into tablets by mixing with pharmaceutically acceptable excipients.
26. Use of controlled release beads according to any one of claims 1-15 in the manufacture
15 of a medicament for the treatment of cardiovascular diseases such as hypertension, congestive heart failure and oedema.
27. A method for the treatment of hypertension, oedemas and congestive heart failure wherein a pharmaceutical formulation according to any one of claims 17-24 is administered
20 to a host in the need of such treatment.

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Fig. 1

Mean diuresis vs midpoint of each time interval (n=12)



INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/01734

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/16, A61K 31/34, A61K 9/20, A61K 9/48
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EMBASE, WPI, WPIL, CLAIMS, CAPLUS, USPATFULL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0361874 A2 (TAKEDA CHEMICAL INDUSTRIES, LTD.), 4 April 1990 (04.04.90), page 2, line 52 - page 4, line 19 --	1-27
X	EP 0475536 A1 (TAKEDA CHEMICAL INDUSTRIES, LTD.), 18 March 1992 (18.03.92), page 3, line 42 - line 46; page 4, line 1 - line 21 --	1-27
X	US 4938968 A (ATUL M. MEHTA), 3 July 1990 (03.07.90), column 2, line 36 - line 40; column 4, line 41 - column 15, line 34, the claims -- -----	1-27

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

8 April 1997

Date of mailing of the international search report

22 -04- 1997

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 96/01734

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 27
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-4 are directed to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been on the alleged effects of the compounds/compositions.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

04/03/97

International application No.

PCT/SE 96/01734

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0361874 A2	04/04/90	SE 0361874 T3 AU 626584 B AU 4233289 A CA 1338596 A DE 68910773 D,T ES 2060784 T IE 63039 B JP 2174931 A JP 8019003 B	06/08/92 05/04/90 17/09/96 11/05/94 01/12/94 22/03/95 06/07/90 28/02/96
EP 0475536 A1	18/03/92	CA 1312548 A DE 3874360 A EP 0277741 A,B SE 0277741 T3 ES 2052697 T JP 8032625 B JP 63301816 A KR 9605138 B US 5026560 A US 5516531 A	12/01/93 15/10/92 10/08/88 16/07/94 29/03/96 08/12/88 22/04/96 25/06/91 14/05/96
US 4938968 A	03/07/90	NONE	